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Why Are There So Many Puzzles in Fighting against COVID-19 Pandemic?

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ABSTRACT

The novel coronavirus (SARS-CoV-2) and its variety that causes coronavirus disease 2019 (COVID-19) have had a great impact on human health and society since it was epidemic in 2019. The traditional immunological theories believe that human body resists the invasion of exogenous substances, such as different kinds of pathogenic microorganisms, through natural immunity and acquired immunity. We have greatly understood the underlying mechanisms of these two kinds of immunities, which are achieved through cellular and humoral immunity. Immune cells mainly include B and T cells. B cells produce specific antibodies and participate in the humoral immune response, while T cells have more extensive immune effects related to the cellular immune response. Therefore, such traditional immunological theories allow us habitually believe that the human body can resist the attack of virus as long as we have established the so-called normal cellular and humoral immune functions, however, in fact, this is not the case. The traditional ideas make us ignore the most critical, but simple and important defense system in our body to fight against the attack of foreign microorganisms, and that is the intracellular potassium ions (K^+) and extracellular sodium ions (Na^+), in particular, the intracellular potassium ions, called "K^+/Na^+ natural immune system". The abnormality of this system, in particular, the intracellular relative deficiency of potassium ions, may have a very important relationship with the susceptibility and pathogenesis of the body to viral infection, and could explain a series of confusing phenomena that appeared during SARS-CoV-2 pandemic and provide new ideas for the prevention and treatment of COVID-19.

1. INTRODUCTION

The novel coronavirus (SARS-CoV-2) and its variety that causes coronavirus disease 2019 (COVID-19)

have had a great impact on human health and society since it was epidemic in 2019. To date, its pandemic has been repeated and has not ended yet. Through the epidemic analysis of SARS-CoV-2 pandemic, the following characteristics and confusion have been noticed [1-5]:

1) Most infected individuals show asymptomatic, some have mild or obvious symptoms, and only a few individuals are seriously ill or die, mainly these people with basic diseases and the elderly;

2) The virus mutates faster;

3) The vaccine can obviously, but not completely prevent the attack of the virus, and the high probability of breakthrough infection occurs;

4) The chemical drugs that can inhibit virus replication may not effectively treat patients;

5) Some natural herbs, including traditional Chinese medicine prescriptions, can have certain curative effects on the infected patients, but their effects cannot be standardized, and the antiviral mechanism is not clear.

For these confusing problems, modern medical knowledge has not yet been able to build a perfect theoretical system to provide more appropriate explanation. Therefore, countries around the world have adopted different strategies, technologies and methods in the process of fighting against this virus, and these have also resulted in different results. At present, human beings strive to end the novel coronavirus pandemic in four ways as follows [6-9]:

1) To resist the invasion of the virus and achieve the purpose of prevention by the development of efficient vaccines;

2) To inhibit virus replication in infected cells and achieve the purpose of treatment by the development of efficient and specific drugs;

3) To defeat the attack of the virus and end the pandemic through the establishment of so-called "herd immunity" based on the natural infection of most people, including those who can't be vaccinated for medical reasons, babies too young to get vaccinated and people on whom the vaccine doesn't work;

4) To strictly control the source of infection and cut off the route of transmission, that is, the current "dynamic zeroing" strategy adopted by China and other countries to prevent the spread of the virus, and then wait for time, hoping to develop better prevention and control methods to end the virus epidemic, or hoping that the pandemic will end in a way that human beings do not know at present.

Why do all this traditional known scientific knowledge, the strategies, means or methods of epidemic prevention and control described in textbooks meet such incomprehensible problems and phenomena in the process of preventing and controlling the COVID-19 pandemic? Therefore, finding new ideas that are different from traditional ones is the key for mankind to prevent and control this virus pandemic and win the battle. Here, I propose a new idea to answer these concerns and try to clarify the key issues of the COVID-19 pandemic that confuse human beings.

2. OUT OF THE IDEOLOGICAL WAY OF TRADITIONAL IMMUNOLOGICAL THEORIES FOR UNDERSTANDING THE MECHANISM OF BODY RESISTANCE TO VIRUS

The traditional immunological theories believe that the human body resists the invasion of exogenous substances, such as different kinds of pathogenic microorganisms, through natural immunity and acquired immunity [10]. Human beings have greatly understood the underlying mechanisms of these two kinds of immunities and proved that they are achieved through cellular and humoral immunity. Immune cells mainly include B and T cells. B cells produce specific antibodies and participate in the humoral immune response, while T cells have more extensive immune effects related to the cellular immune response. Therefore, such traditional immunological theories allow us habitually understand that the human body can resist the attack of virus as long as we establish the so-called normal cellular and humoral immune functions. However, in fact, this is not the case. The traditional ideas make us ignore the most critical, but simple and important defense system in our body against the attack of foreign microorganisms, and that is the intracellular potassium ions (K^+) and extracellular sodium ions (Na^+), called "K^+/Na^+ natural immune system".

Why such a system is so important, but not fully understood and recognized by us? To answer this question, we must first address this issue from the evolution of cell.

There are many kinds of unicellular organisms on the earth and their number is unimaginable. Similarly, bacteria and viruses are everywhere too. The question is how do these unicellular organisms living in different places of nature, such as oceans, lands and lakes, etc., resist the attack of bacteria and viruses? It is not entirely believed that these unicellular organisms can assume the responsibility of resisting bacteria and viruses because they have cell membranes and stronger cell walls. Therefore, unicellular organisms must have constructed a simple and effective system or mechanism to prevent microbial invasion, and I suggest the most important part of this system is a certain concentration of potassium ions (K^+) established within unicellular organisms.

So far, we have known that multicellular animals, especially those that have evolved the nervous system, their bodies have organs, tissues and tissue cells with different functions. An important feature is that these different types of cells can build certain concentrations of intracellular potassium ions, and most aquatic animals living in the sea and freshwater have significantly higher intracellular potassium ions in their cells than those living on land [11]. In addition, the potassium concentrations in excitable cells, such as nerve cells, myocardial cells and muscle cells, etc., are significantly higher than that in other non-excitable cells. For a long time, scientific research has only paid more attention to the excitability of cells with high concentrations of potassium ions because the establishment of a certain concentration of potassium ions in these cells is necessary for these cells to achieve functional activities. Therefore, it is also simply understood that the intracellular potassium ion is only a cofactor to realize cell functional activities, and plays some functional roles like iron, magnesium and calcium ions in cells, for example, maintenance of osmotic pressure balance inside and outside cells [12, 13], maintenance of the basic activities of some biological molecules [14-18], and maintenance of the membrane potential level of excitatory cells [11].

However, it completely ignores its importance in fighting against the attack of microorganisms, especially viruses. It is not known that the potassium ion in cells is the key factor for cells to resist the invasion and attack of foreign microorganisms, which is mainly reflected in the following aspects:

1) Through the high and low concentrations of potassium ion gradient inside and outside the cell, it can establish external positive and internal negative cell membrane potential. In mammalian nerve and muscle cells, such a membrane potential can reach a level of approximately −100 mV, and could be much higher in some marine organisms such as squid because the concentrations of intracellular potassium ions in their excitable cells can reach approximately 400 mM, which is more than twice that of mammalian excitable cells (approximately 140 mM) [11]. The intracellular negative membrane potential established due to the concentration difference of potassium ions inside and outside can prevent microorganisms, such as viruses and bacteria, from contacting cells, that is to say, the body cells can resist the invasion of viruses into cells through the mechanism of biophysical action (bioelectricity) because viruses are usually negatively charged [19-21], which is an important natural immune mechanism;

2) It can prevent the replication of virus in cells, which is a process depending on the concentrations of potassium ions in cells [22]. When the concentrations of intracellular potassium ions are relatively low, it can be conducive to virus replication, while the high concentrations may have inhibitory effect [23-25]. This has been verified in many experiments in vitro, possibly because the low concentration of potassium ion in cells is conducive to viral gene replication;

3) Indirect effect to resist microbial invasion and inhibit its survival, which may be particularly obvious against virus infection;

4) The mechanism of killing and phagocytosis of some cellular immune cells may also be related to the concentrations of potassium ions in cells. High concentrations of potassium ions in cells may be beneficial to the killing and phagocytosis of immune cells [26, 27];

5) In addition to animal cells, plant cells also adapt to survive by establishing similar systems. It is known that intracellular potassium is also a key ion that affects plant growth, maturation and resistance to microbial attack [28-32].

Another important mechanism for animal cells to resist microbial infection is the extracellular so-

dium ions. The concentrations of extracellular sodium ions are determined by the environment. For multicellular organisms that have established independent extracellular fluid systems, such as circulatory systems, the sodium ion concentrations in extracellular fluid are relatively stable, usually close to the concentrations of intracellular potassium ions in the excitable cells. Some lower organisms, such as nematodes, have developed specialized nerve cells that sense the change of environmental sodium ions and determine whether the surrounding environment is suitable for their own survival [33].

It is obvious that most microorganisms, including viruses, need a certain concentration of suitable ions to survive. For animals, it has been recognized that a certain concentration of extracellular sodium ions can resist the invasion of microorganisms. For example, in human body, the development of perforated appendicitis is related to the relatively low blood sodium [34-37]. It was also found that the seasonal low blood sodium of an American bat was related to its infection with a coronavirus and massive death [38, 39]. A previous study also found that significant low blood sodium and relatively low blood potassium ion levels are significantly associated with the development of severe illness and death in COVID-19 patients [40].

Human beings have a long history of taking salt through food. It is known that mankind lives better by providing appropriate salt through diet, which may also be important progress for human to resist natural microbial attacks. However, with the development of modern medicine, there is a deviation in the cognition of extracellular sodium ions. Due to the emergence of some chronic human diseases and repeated observations in animal experiments, sodium has become the scapegoat for the occurrence of these diseases. Some popular health care and preventive medicine views believe that high-salt diet is related to several chronic diseases, such as hypertension, diabetes and obesity, etc., while low sodium intake is beneficial to prevent the occurrence and development of such diseases [41-46]. Therefore, in the past few decades, especially in developed countries, considerable efforts have been made to emphasize a low-salt diet [47-49]. As a result, some groups of human beings may result in relatively deficient of sodium from the beginning of the embryo to the elderly. This may provide an important window for virus attack in these populations.

3. K^+/NA^+ SYSTEM IS THE KEY FOR CELLS TO ACHIEVE NON-SPECIFIC NATURAL IMMUNITY

Based on the above analysis, it can be believed that the abnormal K^+/Na^+ system, mainly the occurrence of relative deficiency of intracellular potassium and extracellular sodium ions, may be the core factor leading to the susceptibility of the virus, however, why can the relative deficiency of K^+/Na^+ ions, especially the intracellular potassium ions, lead to such serious consequences? This needs to be explained from the causes of the relative deficiency of potassium ions in cells.

The relative deficiency of intracellular potassium is usually difficult to attract sufficient attention. On the one hand, the current technologies are difficult to accurately detect and evaluate the concentrations of potassium ions in living organs, tissues and cells. Detecting the concentrations of potassium ions in body fluids, such as blood, can only indirectly reflect the dynamic changes of potassium ions, but not the overall storage of potassium ions in the body. Because the concentrations of potassium ions in body fluid are affected by many factors, the deficiency of intracellular potassium can be manifested and detected only when the body has had serious deficiencies and obvious symptoms of disease. Therefore, to understand the relative deficiency of potassium ions in the body cells, we need to analyze from the storage and dynamic distribution of potassium ions in organs, tissues and tissue cells. If all cells in the body reach the normal concentrations of intracellular potassium ions required by the cells themselves, it is perfect, however, the actual situation may be completely beyond our understanding because: 1) A certain proportion of cells may not reach the normal or ideal concentrations; 2) The storage and utilization of potassium ions between cells are competitive, which depends on the amount and activity of Na, K-ATPase on the cell membrane [50-57]; 3) The storage and utilization of potassium ions between organs and tissues are also competitive with each other; 4) Excitatory cells, such as nerve cells, myocardial cells and muscle cells, have competitive

advantage in the storage and utilization of potassium ions; 5) For the nervous system, it has been found that the concentrations of potassium ions in various cells are not exactly the same in different brain areas and even in the same brain region, which can be detected by using electrophysiological techniques to record membrane potentials [58, 59]. The situation is true for cardiomyocytes and muscle cells; 6) The storage and utilization of potassium ions in non-neural tissue cells can be regulated by neural activities and endocrine regulatory factors [55]; 7) The concentrations of potassium ions in muscle cells are related to and regulated by the activities of muscle cells; 8) Biological rhythm mechanism, such as activity/sleep cycle, may play an important role in regulating the competitive transfer of potassium ions between organs, tissues and tissue cells; 9) The potassium content in the diet and the absorption efficiency of the digestive system may play an important role in affecting the storage of potassium ions in the body; 10) The cosmic mechanism, especially the Brownian motion whose physical mechanism is still unknown, may play a role in regulating the efficiency of cell Na-K-ATPase activity and affect the storage of potassium ions in cells. Such a mechanism may be related to cosmic dark energy, but not an ATP bioenergy-dependent process based on a theoretical analysis [60].

Therefore, if the potassium ions entering the body through diet are less than the discharged ones and cannot reach a dynamic balance, it will lead to a relative deficiency of potassium ions in the body. However, the relative deficiency of potassium ions in the body cells is not easy to attract attention. An important reason is that some of the mechanisms described above can temporarily achieve the dynamic redistribution of potassium ions between the different organs, tissues and tissue cells to a certain extent. Therefore, the relative deficiency of potassium ions often only appears in some organs and tissues. A high probability is that nerve system can transfer potassium ions from other tissues of the body into nerve tissue and cells through neural activity regulation, such as exercise, stress and endocrine changes, so as to give priority to meeting the needs of nerve cells, while the competitive use of potassium ions can also be achieved by the transfer between non-nerve tissues and cells, and such a process depends on the ability and efficiency of the tissues and cells to obtain competitively potassium ions from the blood and extracellular fluid containing low concentrations of potassium ions (3 - 5 mM). If the potassium ions absorbed by the body through diet cannot meet the overall needs of the body, the competitive storage and utilization may lead to the relative deficiency of potassium ions in certain tissues and cells. Such a competitive advantage and the distribution and use mechanism of potassium ions in the body cells should be controlled by the genes of tissues and cells, which should not be difficult to understand because such a competitive process may mainly depend on the content and activity efficiency of Na, K-ATPase on the cell membrane [57].

4. THE RELATIONSHIP BETWEEN THE RELATIVE DEFICIENCY OF POTASSIUM IONS IN HUMAN BODY AND VIRAL INFECTION

The relative deficiency of extracellular sodium ions and intracellular potassium ions in the body provides an important theoretical explanation for our understanding of the body's resistance to microbial attacks, especially viral infection, and may also be an important reason for the emergence of different diseases, such as Alzheimer's disease, Parkson's disease, depression, tumors and cancers, etc., which will be described in details in other papers [61]. Therefore, a reasonable explanation for the epidemic characteristics of SARS-CoV-2 in the population and the severity of COVID-19 can be provided. An individual accompanied by hyponatremia and the relative deficiency of potassium ions in the cells of the respiratory system will significantly improve the susceptibility of COVID-19 and the severity of the progression of the disease. The infection of other viruses in various organs, tissues and cells may also have a similar mechanism.

It is clear that if the body has a normal K^+/Na^+ natural immune system, and even if infected with SARS-CoV-2, an individual will only show asymptomatic infection, which is a typical epidemic characteristic of this virus. On the contrary, if individuals including some infants, the elderly and people with basic diseases exist a low level of extracellular sodium and a relative deficiency of intracellular potassium, particularly in the respiratory system, then the virus will easily break through the K^+/Na^+ natural defense sys-

tem, infect the cells with relative deficiency of intracellular potassium ions and replicate in these cells. In addition, the relative deficiency of intracellular potassium ions may be an important factor to accelerate the replication of the virus in these cells, while the cells with the normal intracellular potassium ions may inhibit the replication of the invaded viruses.

5. NEW STRATEGIES TO COMBAT THE SARS-COV-2 PANDEMIC

Therefore, the above statements based on discussion and analysis will enable us to establish new strategies to combat the SARS-CoV-2 pandemic. Maintaining the integrity of the K^+/Na^+ natural defense system in population is the primary way. To correct the hyponatremia and the relative deficiency of potassium in some populations, which may result in insufficient sodium and potassium content in diet, appropriate eating habits and inappropriate "scientific knowledges", is the key way. Through reasonable diet and living habits or appropriate treatment including natural herbs by directly providing potassium intake, the ability of people to fight against virus infection including SARS-CoV-2 will be greatly strengthened. On this basis, we will expect to end more effectively SARS-CoV-2 pandemic and prevent its recurrence combing with vaccine immunization to consolidate the fortress of the body against SARS-CoV-2 infection. It should be emphasized that the development of new drugs will only be a treatment for a small number of infected patients who may not be able to quickly correct the imbalance of the K^+/Na^+ system through diet and other methods, especially the obvious relative deficiency of intracellular potassium ions in the body.

6. CONCLUSION AND SIGNIFICANCE

The confusion caused by the COVID-19 pandemic allows me to point out the K^+/Na^+ natural immune (defense) system against virus infection, which is formed naturally based on cell evolution and may play a key role in combating viral infection and inhibiting viral replication. The abnormal conditions of this system, in particular, the relative deficiency of intracellular potassium ions provide new ideas for explaining the confusion of the COVID-19 pandemic and put forward new strategies and suitable measures for the control, treatment and prevention of this disease. The statements and discussion in this paper will also raise new ideas for further understanding the physiological mechanisms of life and the pathophysiological mechanisms of diseases in nervous and non-nervous systems.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest regarding the publication of this paper.

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